Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Cryptosporidiosis (Last updated June 17, 2013; last reviewed May 7, 2013)

Epidemiology

Cryptosporidiosis is caused by various species of the protozoan parasite *Cryptosporidium*, which infect the small bowel mucosa and, if symptomatic, typically cause diarrhea. *Cryptosporidium* can also infect other gastrointestinal and extraintestinal sites, especially in individuals whose immune systems are suppressed. Advanced immunosuppression—typically CD4 T lymphocyte cell (CD4) counts of <100 cells/μL[1]—is associated with the greatest risk for prolonged, severe, or extraintestinal cryptosporidiosis. The three species that most commonly infect humans are *Cryptosporidium hominis*, *Cryptosporidium parvum*, and *Cryptosporidium meleagridis*. Infections are usually caused by one species, but a mixed infection is possible.[2]

Cryptosporidiosis remains a common cause of chronic diarrhea in AIDS patients in developing countries, with up to 74% of diarrheal stools demonstrating the organism.[3] In developed countries with low rates of environmental contamination and where potent antiretroviral therapy (ART) is widely available, cryptosporidiosis has decreased and occurs at an incidence of <1 case per 1000 person-years in patients with AIDS.[4] Infection occurs through ingestion of *Cryptosporidium* oocysts. Viable oocysts in feces can be transmitted directly through contact with infected humans or animals, particularly those with diarrhea. Oocysts can contaminate recreational water sources such as swimming pools and lakes, and public water supplies and may persist despite standard chlorination (see Appendix: Food and Water-Related Exposures). Person-to-person transmission is common, especially among sexually active men who have sex with men.

Clinical Manifestations

Patients with cryptosporidiosis most commonly have acute or subacute onset of watery diarrhea, which may be accompanied by nausea, vomiting, and lower abdominal cramping. Severity can range from asymptomatic to profuse, cholera-like diarrhea. More severe symptoms tend to occur in immune-suppressed patients, whereas transient diarrhea alone is typical in hosts with competent immune systems. Fever is present in approximately one-third of patients and malabsorption is common. The epithelium of the biliary tract and the pancreatic duct can be infected with *Cryptosporidium*, leading to sclerosing cholangitis and to pancreatitis secondary to papillary stenosis, particularly among patients with prolonged disease and low CD4 cell counts.[5-8] Pulmonary infections also have been reported,[9,10] and may be under-recognized.[11]

Diagnosis

Diagnosis of cryptosporidiosis can be made by microscopic identification of the oocysts in stool or tissue with acid-fast staining or direct immunofluorescence, which offers better sensitivity.[12] Immunofluorescence is estimated to be 10 times more sensitive than acid-fast staining and is now the gold standard for stool examination. Concentration methods (i.e., formalin ether or formalin-ethyl acetate) and flotation methods (i.e., Sheather's sucrose or sodium chloride) may facilitate diagnosis, but they are very labor intensive and not routinely used in clinical laboratories. Antigen-detection by enzyme-linked immunosorbent assay or immunochromatographic tests also are useful, with sensitivities reportedly ranging from 66% to 100%, depending on the specific test. Molecular methods such as polymerase chain reaction (PCR) are even more sensitive,[13] detecting as few as five oocysts in spiked stool samples and nearly double the number of cases identified by microscopic methods. Cryptosporidial enteritis also can be diagnosed from small sections from intestinal biopsy.

A single stool specimen is usually adequate for diagnosis in individuals with profuse diarrheal illness, whereas repeat stool sampling is recommended for those with milder disease.

Preventing Exposure

HIV-infected individuals should be educated and counseled about the different ways that *Cryptosporidium* can be transmitted **(BIII)**. Modes of transmission include having direct contact with infected adults, diaper-aged children, and infected animals; coming into contact with contaminated water during recreational activities; drinking contaminated water; and eating contaminated food.

Detailed prevention recommendations related to food and water exposures (including methods for removing *Cryptosporidium* from drinking water), pet exposures, and travel-related exposures can be found in Appendix A: Recommendations to Help HIV-infected Patients Avoid Exposure to, or Infection from, Opportunistic Pathogens.

Scrupulous handwashing can reduce the risk of diarrhea in HIV-infected individuals, including diarrhea caused by *Cryptosporidium*.[14] HIV-infected patients should be advised to wash their hands after potential contact with human feces (including after diapering small children). Hand-washing also should be recommended in association with the following activities: after handling pets or other animals, gardening or having other contact with soil; before preparing food or eating; and before and after sex **(BIII)**. HIV-infected patients should avoid unprotected sex, especially practices that could lead to direct (e.g., oral-anal) or indirect (e.g., penile-anal) contact with feces. They should be advised to use barriers such as condoms and dental dams during sex to reduce such exposures **(BIII)**.

HIV-infected individuals—particularly those with CD4 counts <200 cells/μL—should avoid direct contact with diarrhea or stool from pets **(BIII)**. Gloves should be worn when handling feces or cleaning areas that might have been contaminated by feces from pets **(BIII)**. They should also limit or avoid direct exposure to calves and lambs **(BII)**. Paying attention to hygiene and avoiding direct contact with stool are important when visiting premises such as farms or petting zoos where these animals are housed or exhibited.

HIV-infected individuals should not drink water directly from lakes or rivers **(AIII)**. Waterborne infection also can result from swallowing water during recreational activities. HIV-infected individuals should be made aware that lakes, rivers, and salt water beaches and some swimming pools, recreational water parks, and ornamental water fountains may be contaminated with human or animal waste that contains *Cryptosporidium*. They should avoid swimming in water that is likely contaminated and should avoid swallowing water while swimming or playing in recreational water **(BIII)**.

Outbreaks of cryptosporidiosis have been linked to drinking water from municipal water supplies. During outbreaks or in other situations that impose a community advisory to boil water, boiling water for at least 1 minute will eliminate the risk for cryptosporidiosis **(AIII)**. Using submicron personal-use water filters (home/office types) or bottled water also may reduce the risk of infection from municipal and well water **(BII)**.

For persons with low CD4 cell counts, the magnitude of the risk of acquiring cryptosporidiosis from drinking water in a non-outbreak setting is uncertain, and available data are inadequate to recommend that all HIV-infected persons boil water or avoid drinking tap water in non-outbreak settings. However, HIV-infected individuals should consider drinking only filtered water **(CIII)**, despite the complexities involved in selecting appropriate products, the lack of enforceable standards for removal of oocysts, the costs of the products, and the logistic difficulty of using these products consistently. Note that ice made from contaminated tap water also can be a source of infection.

HIV-infected patients with low CD4 cell counts should be cautious about eating raw oysters because cryptosporidial oocysts can survive in oysters for longer than 2 months and have been found in oysters taken from certain commercial oyster beds **(CIII)**. In the hospital setting, standard precautions for use of gloves and for hand-washing after removal of gloves should be sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible HIV-infected individual **(BIII)**. Because of the potential for fomite transmission, some specialists recommend that HIV-infected patients, especially individuals who are severely immunocompromised, not share a room with a patient with cryptosporidiosis **(CIII)**.

HIV-infected individuals who travel to developing countries should be warned to avoid drinking tap water or

using tap water to brush their teeth **(BIII)**. Ice that is not made from bottled water and consumption of raw fruits or vegetables that could have been washed in tap water should also be avoided **(BIII)**. HIV-infected individuals also should avoid other sources of *Cryptosporidium* oocysts as much as possible **(BIII)**. These include working directly with people with diarrhea; with farm animals such as cattle and sheep; and with domestic pets that are very young or have diarrhea. If exposure is unavoidable, gloves should be used and practices for good hand hygiene observed.

Preventing Disease

Because chronic cryptosporidiosis occurs primarily in patients with advanced immunodeficiency, appropriate initiation of combination ART before the patient becomes severely immunosuppressed should prevent this disease **(AII)**. Rifabutin and possibly clarithromycin, when taken for *Mycobacterium avium complex* prophylaxis, have been found to protect against cryptosporidiosis.[15,16] Data are insufficient, however, to warrant a recommendation for using rifabutin or clarithromycin as chemoprophylaxis for cryptosporidiosis.

Treating Disease

In the setting of severe immune suppression, ART with immune restoration to a CD4 count >100 cells/μL usually leads to resolution of clinical cryptosporidiosis[17-21] and is the mainstay of treatment. Therefore, patients with cryptosporidiosis should be started on ART as part of the initial management of their infection **(AII)**. HIV protease inhibitors (PIs) can inhibit *Cryptosporidium in vitro* and in animal models, and some experts believe that PI-based ART is preferable in patients with documented cryptosporidiosis **(CIII)**.[22,23] Management should also include symptomatic treatment of diarrhea with anti-motility agents **(AIII)**. Tincture of opium may be more effective than loperamide **(CIII)**. Octreotide, a synthetic octapeptide analog of naturally occurring somatostatin that is approved to treat secreting tumor-induced diarrhea, is no more effective than other oral antidiarrheal agents and is usually **not** recommended **(CII)**.[24] Because diarrhea can cause lactase deficiency, patients should avoid milk products **(CIII)**.

Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with AIDS, often requiring intensive support. Oral rehydration should be pursued aggressively with oral rehydration solutions **(AIII)**.

Patients with biliary tract involvement may require endoscopic retrograde choledocoduodenoscopy for diagnosis. They may also benefit from sphincterotomy and/or stenting.[25]

Several agents have been investigated in small, randomized controlled clinical trials of HIV-infected adults, including nitazoxanide, paromomycin, spiramycin, bovine hyperimmune colostrum, and bovine dialyzable leukocyte extract. No pharmacologic or immunologic therapy directed specifically against *Cryptosporidium* has been shown to be consistently effective when used without ART.[19]

Nitazoxanide is an orally administered nitrothiazole benzamide with *in vivo* activity against a broad range of helminths, bacteria, and protozoa.[26,27] It is approved by the U.S. Food and Drug Administration for treatment of cryptosporidiosis in children and adults. When administered for 3 days at 500 mg twice daily to HIV-uninfected adults with cryptosporidiosis, nitazoxanide resulted in higher rates of diarrhea resolution and oocyst-free stools than placebo.[26] In one study, HIV-infected adults with cryptosporidiosis with CD4 counts >50 cells/μL were treated with nitazoxanide 500 to 1000 mg twice daily for 14 days; they experienced substantially higher rates of parasitological cure and resolution of diarrhea than those in the placebo group.[27] This finding was not confirmed, however, in two randomized trials in children.[28,29] Data from a compassionate use program before the advent of potent ART, which included primarily white male adults with median CD4 counts less than 50 cells/μL, reported that a majority of patients experienced some degree of clinical response (reduction in frequency of total stool and of liquid stools), usually within the first week of treatment.[30] Adverse events associated with nitazoxanide are limited and typically mild, and no important drug-drug interactions have been reported. Because of the clinical significance of cryptosporidiosis, a trial of

nitazoxanide or other anti-parasitic drugs in conjunction with ART, but never instead of ART, can be considered **(CIII)**.

Paromomycin is a non-absorbable aminoglycoside indicated for the treatment of intestinal amebiasis but not specifically approved for cryptosporidiosis. It is effective in high doses for the treatment of cryptosporidiosis in animal models.[31] A meta-analysis of 11 published studies of paromomycin in humans reported a response rate of 67%; however, relapses were common, with long-term success rates of only 33%.[25] Two randomized trials comparing paromomycin with placebo among patients with AIDS and cryptosporidiosis showed that the drug had limited effectiveness in patients with AIDS,[32,33] and a meta-analysis of the two trials found the drug was not significantly more effective than placebo at reducing diarrheal frequency or parasite burden, but that analysis was limited by the small sample size and methodologic problems.[19] One case series suggested a better response rate in patients receiving paromomycin along with ART.[34] Paromomycin may be used instead of nitazoxanide along with, but never instead of ART **(CIII)**.

Special considerations with regard to starting ART

As noted above, patients with cryptosporidiosis should be offered ART as part of the initial management of their infection **(AII)**. PIs can inhibit *Cryptosporidium in vitro* and in animal models, thus some authorities feel that PI-based ART is preferable in patients with documented cryptosporidiosis **(CIII)**.[22,23]

Monitoring of response to therapy and adverse events (including IRIS)

Patients should be monitored closely for signs and symptoms of volume depletion, electrolyte imbalance, weight loss, and malnutrition. Total parenteral nutrition may be indicated in certain patients **(CIII)**. Immune reconstitution inflammatory syndrome (IRIS) has not been described in association with treatment of cryptosporidiosis.

Managing treatment failure

Supportive treatment and optimization of ART to achieve full virologic suppression are the only feasible approaches to managing treatment failure **(AIII)**.

Preventing Recurrence

No pharmacologic interventions are known to be effective in preventing the recurrence of cryptosporidiosis.

Special Considerations During Pregnancy

Rehydration and initiation of ART are the mainstays of initial treatment of cryptosporidiosis during pregnancy, as they are in non-pregnant women **(AII)**. Pregnancy should not preclude the use of ART and in fact is always an indication for ART.[35] Nitazoxanide is not teratogenic in animals but no human data on use in pregnancy are available. Nitazoxanide can be used in pregnancy after the first trimester in women with severe symptoms **(CIII)**. Limited information is available about the teratogenic potential of paromomycin, but oral administration is associated with minimal systemic absorption, which may minimize potential risk. Paromomycin can be used in pregnancy after the first trimester in women with severe symptoms **(CIII)**. Loperamide is poorly absorbed and has not been associated with birth defects in animal studies. However, a recent study identified an increased risk of congenital malformations, and specifically hypospadias, among 683 women with exposure to loperamide early in pregnancy.[36] Therefore, loperamide should be avoided in the first trimester, unless benefits are felt to outweigh potential risks **(CIII)**. Loperamide is the preferred anti-motility agent in late pregnancy **(CIII)**. Opiate exposure in late pregnancy has been associated with neonatal respiratory depression, and chronic exposure may result in neonatal withdrawal, therefore tincture of opium is **not** recommended in late pregnancy **(AIII)**.

Recommendations for Preventing and Managing Cryptosporidiosis

Preventing Chronic Cryptosporidiosis

- Because chronic cryptosporidiosis occurs primarily in persons with advanced immunodeficiency, initiation of ART before the patient becomes severely immunosuppressed should prevent the disease **(AII)**.

Managing Cryptosporidiosis

Preferred Management Strategies:

- Initiate or optimize ART for immune restoration to CD4 count >100 cells/mm^3 **(AII)**.
- Aggressive oral and/or IV rehydration and replacement of electrolyte loss **(AIII)**, and symptomatic treatment of diarrhea with anti-motility agent **(AIII)**.
- Tincture of opium may be more effective than loperamide as an anti-diarrheal agent **(CIII)**.

Alternative Management Strategies:

No therapy has been shown to be effective without ART. Trial of these agents may be used in conjunction with, but not instead of, ART:

- Nitazoxanide 500–1000 mg PO BID with food for 14 days **(CIII)** + optimized ART, symptomatic treatment, and rehydration and electrolyte replacement, *or alternatively*
- Paromomycin 500 mg PO QID for 14 to 21 days (**CIII)** + optimized ART, symptomatic treatment and rehydration and electrolyte replacement

Other Considerations:

- Since diarrhea can cause lactase deficiency, patients should avoid milk products **(CIII)**.

Key to Acronyms: ART = antiretroviral therapy; IV = intraveneously; PO = orally; BID = twice a day; QID = four times a day

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